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(54) TACKY ADHESIVE COMPOSITION FOR MEDICAL TREATMENT

(57)Abstract:
PROBLEM TO BE SOLVED: To embody sufficient tacky adhesives and the decreases the reshes of the skin and the pain at the time of peeling by constituting the tacky adhesive compsn. of an acrylic copolymer and aliphat. alcohol and composing the acrylic copolymer of 2-ethyl hexyl methacrulate and alkyl ester acrylate exclusive of the methactuylate.
SOLUTION: This tacky adhesive compsn. for medical treatment consists of 88 to 99.5wt.%. acrylic copolymer and 0.5 to 20wt.% 12 to 20C aliphat. alcohol. The acrylic copolymer consist of the 2-ethyl hexylmethacrylate and the alkyl ester (meth) acrylate of 6 to 16C alkyl groups exclusive of the 2-ethyl hexyl methacylate as its constituting components and contains 40 to 90wt.% 2-ethyl hexyl methacrylate in the monomer components constituting the acrylic copolymer. Then, the higher alcohol is added to the acrylic copolymer, by which the stimuli on the skin are decreased. In addition, the tacky adhesive layer is softened, by which both properties of a hydrophilic property and hydrophobic property are imparted to the tacky adhesive compsn.

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* NOTICES *

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CLAIMS

[Claim(s)]
[Claim 1] It is the medical-application adhesiveness constituent which is a medical-application adhesiveness constituent which consists of 80 - 99.5 % of the weight of acrylic copolymers, and 0.5 - 20 % of the weight of fatty alcohol of carbon numbers 12-20, and this acrylic copolymer makes a constituent 2-ethylhexyl methacrylate and the acrylic-acid (meta) alkyl ester of the carbon numbers 6-16 of the alkyl group except it, and is characterized by containing 2-ethylhexyl methacrylate 40 to 90% of the weight in the monomer component which constitutes an acrylic copolymer.
[Claim 2] The medical-application adhesiveness constituent according to claim 1 characterized by containing a drug.
[Claim 3] The medical-application adhesiveness constituent according to claim 1 or 2 characterized by higher alcohol being cetyl alcohol.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] To the skin, this invention is low stimulative and relates to an adhesive good medical-application adhesiveness constituent.
[0002]
[Description of the Prior Art] The approach of making the inside of the body absorbing a drug from the skin is characteristic in respect of the ability to stop administration on the way, when ** side effect that a standup with rapid ** drug blood drug concentration is suppressed and that the metabolic turnover in ** liver is avoidable is remarkable. Since especially the patches used for such a purpose are excellent in durability compared with ointment, patches-ization is tried about various drugs. However, when using patches, the skin stimulus poses a big problem. There were the thing of sensitization nature and primary stimulative one by contact in a skin stimulus, even if it used the ingredient which does not start sensitization, after removing patches, redness might remain and pigmentation might be produced.
[0003] On the other hand, examination for reduction-izing a skin stimulus by the approach of former versatility is performed. For example, to JP,6-256183,A, melting mixing of polyoxy alkylene glycol and its block copolymer is carried out into a binder, the moisture permeability of the whole pharmaceutical preparation is raised by applying to base materials, such as a nonwoven fabric which has moisture permeability, and the approach of reduction-izing a stimulus is indicated.
[0004] However, in this approach, it is difficult to give absorptivity sufficient in the condition of having blended with patches only by an additive having absorptivity. That is, when the water excretion rate from the skin changes with situations, for example, it sweats in large quantities, it is difficult to give only the moisture permeability which corresponds promptly, and the effectiveness can seldom be expected.
[0005] Moreover, for example, the method of reducing the exfoliation force is proposed by JP,7-206710,A by considering as a presentation to which the hygroscopic matter in a binder remains in a hide skin surface at the time of exfoliation. However, this approach was not enough as the effectiveness which **** may occur on a skin front face with the moisture held with the hygroscopic matter during pasting, and reduction-izes a skin stimulus, although the skin injury at the time of exfoliation could be reduced to be sure.
[0006]
[Problem(s) to be Solved by the Invention] This invention does not solve the above-mentioned trouble, and the purpose does not have a bad influence on emission of a drug, but moreover discovers adhesiveness sufficient during pasting, and is for the rash of the skin and the pain at the time of exfoliation to offer few medical-application adhesiveness constituents.
[0007]
[Means for Solving the Problem] It consists of 80 - 99.5 % of the weight of acrylic copolymers, and 0.5 - 20 % of the weight of fatty alcohol of carbon numbers 12-20, this acrylic copolymer makes a constituent 2-ethylhexyl methacrylate and the acrylic-acid (meta) alkyl ester of the carbon numbers 6-16 of the alkyl group except it, and the medical-application adhesiveness constituent of this invention is characterized by containing 2-ethylhexyl methacrylate 40 to 90% of the weight in the

monomer component which constitutes said acrylic copolymer.
[0008] The medical-application adhesiveness constituent of this invention consists of an acrylic copolymer and fatty alcohol, and this acrylic copolymer makes a constituent 2-ethylhexyl methacrylate and the acrylic-acid alkyl ester except it (meta).
[0009] As acrylic-acid alkyl ester used by this invention (meta), the thing of the carbon numbers 6-16 of an alkyl group is used. Since the cohesive force of the acrylic copolymer with which the carbon number of an alkyl group is obtained less than by six becomes small too much, when long duration pasting is carried out to the skin, it becomes the cause of the paste remainder. Moreover, if the carbon number of an alkyl group exceeds 16, the solubility of the fatty alcohol mentioned later will fall and sufficient adhesive ability will no longer be demonstrated.
[0010] As such (meta) acrylic-acid alkyl ester, 2-ethylhexyl acrylate, hexyl (meta) acrylate, heptyl (meta) acrylate, octyl (meta) acrylate, dodecyl (meta) acrylate, stearyl (meta) acrylate, etc. are mentioned, for example.
[0011] Among the component which constitutes the acrylic copolymer used by this invention, the rate of 2-ethylhexyl methacrylate is restricted to 40 - 90% of the weight, and is 60 - 80 % of the weight preferably. By making the amount of 2-ethylhexyl methacrylate used into the above-mentioned range, when fatty alcohol is blended, good stickiness is discovered.
[0012] A polyfunctional monomer may be added by the above-mentioned acrylic copolymer. The above-mentioned polyfunctional monomer raises internal cohesive force, and in order to obtain patches without the paste remainder, it is added in the range which does not have a bad influence on the emission nature of a drug, or skin low stimulative ones. Polyalkylene glycols [, such as a polymethylene-glycol; polyethylene glycol], such as hexamethylene glucohol which is made to react with an acrylic acid (meta) and is obtained as such a polyfunctional monomer; di(meth)acrylate, such as a glycerol and pentaerythritol, Tori (meta) acrylate, tetrapod (meta) acrylate, etc. are used suitably.

[0013] When it decreases, effectiveness is not acquired, but since a binder will lifting-come to be easy of gelation if it increases, 0.005 - 0.5 % of the weight is desirable [the amount of the above-mentioned polyfunctional monomer used] among the above-mentioned acrylic copolymer.
[0014] The polymerization of the above-mentioned acrylic copolymer is carried out by the usual well-known approach, for example, it blends the above-mentioned monomer under existence of a polymerization initiator, and is prepared by performing solution polymerization. However, polymerization conditions are mainly suitably chosen by the class of monomer.
[0015] The fatty alcohol used by this invention is restricted to the thing of carbon numbers 12-20. Volatility becomes [a carbon number] high less than by 12, and compatibility with the above-mentioned acrylic copolymer becomes low. Moreover, if a carbon number exceeds 20, hydrophobicity will become high too much and sufficient effectiveness will no longer be acquired.
[0016] As such fatty alcohol, lauryl alcohol, myristyl alcohol, cetyl alcohol, stearyl alcohol, the cetostearyl alcohol, OIRERU alcohol, etc. are mentioned, these may be used independently and two or more sorts may be used together, for example. Especially in these, cetyl alcohol is desirable.
[0017] In the medical-application adhesiveness constituent of this invention, the content of the above-mentioned fatty alcohol is restricted to 0.5 - 20% of the weight, and is 1 - 7 % of the weight preferably. Effectiveness with the content of fatty alcohol sufficient at less than 0.5 % of the weight is not acquired, but if it increases, adhesion physical properties will fall and the paste remainder and peeling will become easy to take place at the time of pasting.
[0018] A plasticization agent, absorption enhancers, a stabilizing agent, a bulking agent, etc. may be blended with the above-mentioned medical-application adhesiveness constituent if needed.
[0019] The above-mentioned plasticization agent raises the diffusion rate in the adhesive constituent of the below-mentioned drug, and raises the drug absorbed amount to the skin at the same time it adjusts the stickiness of the above-mentioned adhesive constituent. as the above-mentioned plasticization agent -- ester [with fatty acids, such as hydrocarbon; myristic-acid isopropyls, such as a liquid paraffin, a mono-lauric-acid glycerol, and sebacic-acid diethyl univalent, or polyhydric alcohol]; -- in addition to this, fats and oils of the natural product origin, such as lanolin and olive oil, etc. are mentioned.
[0020] Since stickiness will worsen if effectiveness is not discovered and increases if it decreases,

the loadings of the above-mentioned plasticization agent have 1 - 15 desirable % of the weight among the above-mentioned adhesive constituent.
[0021] What raises the hydration of the thing; skin which is used in order that the above-mentioned absorption enhancers may act on the skin and may raise the skin permeability of a drug, and makes structure of the skin loose; it is classified into what serves as a carrier who dissolves a drug good and carries in the skin. As absorption enhancers, polysorbate, lauric-acid diethanolamide, a lauroyl sarcosine, polyoxyethylene alkyl ether, polyoxyethylene alkylamine, etc. are mentioned, and these are used in the range which worsens neither stickiness nor skin irritation, for example.
[0022] the above-mentioned stabilizing agent is used in order to suppress oxidization and decomposition of a drug or other components and to prevent aging of pharmaceutical preparation -- having -- for example, anti-oxidant [, such as butylhydroxytoluene and a sorbic acid,]; -- in addition to this, cyclodextrin, ethylenediaminetetraacetic acid, etc. are mentioned.
[0023] The above-mentioned bulking agent is used for a binder layer, a reservoir layer, etc. for sticky accommodation, and homogeneity distribution and maintenance of drugs, for example, a calcium carbonate, titanium oxide, a lactose, crystalline cellulose, a silicic acid anhydride, etc. are mentioned.
[0024] A drug may be blended with the above-mentioned adhesive constituent. Various approaches can be adopted as combination of a drug, for example, it may be made to dissolve in a binder layer, and it may be blended where powder is carried out for a part. Moreover, it may be blended in the condition of having been enclosed with the microcapsule etc., and the reservoir layer of a drug may be prepared apart from a binder layer. When making a binder layer dissolve or distribute a drug, it is blended in the range which does not spoil the stickiness of a binder layer, and the loadings are desirable 0.1 to 30% of the weight among a binder layer.
[0025] if it applies to the skin and is absorbed by the inside of the body as the above-mentioned drug, it will limit especially -- not having -- for example, steroid hormone agents, such as vasodepressor; estradiols, such as hypotensor; nitroglycerin, such as nifedipine and clo JININ, and isosorbide dinitrate, and progesterone, -- antihistamines, such as steroid system anti-inflammatory agent; diphenhydramine, such as antiphlogistic sedative drug; prednisolones, such as narcotic; indomethacins, such as; lidocaine, and ketoprofen, and dexamethasone, and chlorpheniramine, etc. are mentioned.
[0026] Although it can prepare according to the conventional method of adhesive tape manufacture, for example, a solvent coating method, a hot melt coating method, an electron ray hardening emulsion coating method, etc. can be used in order to manufacture patches using the medical-application adhesiveness constituent of this invention, a solvent coating method is desirable especially. By the describing [above] solvent coating method, the patches by which the binder layer of predetermined thickness was formed on the base material can be obtained by blending the additive of a drug and others with the above-mentioned adhesive constituent if needed, applying to base material one side, and removing a solvent by desiccation. Moreover, after once carrying out coating of the above-mentioned adhesive constituent (the additive of a drug and others is included if needed) on a releasing paper, making it dry and forming a binder layer, the laminating of the binder layer may be imprinted and carried out to a base material.
[0027] That it was not limited, for example, the film of polyethylene terephthalate carried out [that etc.] siliconizing especially as the above-mentioned releasing paper is used.
[0028] What has the flexibility which can follow in footsteps of a motion [a skin front face], and the barrier nature which prevents loss of the additive of a drug and others as the above-mentioned base material is used suitably. As such a base material, it may be used with which gestalt of a monolayer film made from polyethylene, polypropylene, an ethylene-vinylacetate copolymer, ethylene and (meta) a methyl-acrylate copolymer, a polyvinyl chloride, a polyvinylidene chloride, nylon, polyester, etc., a porosity film, nonwoven fabrics or these layered products, and an aluminum vacuum evaporationo film, for example.
[0029]
[Function] Since the acrylic copolymer used by this invention does not have any polar groups other than ester, it is extremely stable and stimulative [chemical] does not contain a high compound to the skin. Moreover, by adding higher alcohol to the above-mentioned acrylic copolymer, the stimulus to the skin can be reduced more, a binder layer is softened, and the adhesive constituent equipped

with the property of both a hydrophilic property and hydrophobicity is obtained. Furthermore, it has a high moisturizincy effect to fatty alcohol itself and the skin.
[0030] Although the medical-application adhesiveness constituent of the reason for reducing the stimulus to the skin of this invention is not clear, it thinks as follows.
** The physical properties of an adhesive constituent cannot give a stimulus easily to the skin during pasting.
** Absorb moisture and excrement good from ****** by the acrylic copolymer and balance of the hydrophobicity and the hydrophilic property of fatty alcohol.
** It is rare to receive the mechanical stimulus of keratin exfoliating when removing, or hair being plucked off and pulling the skin, and even if keratin exfoliation in a skin front face arises further, the damage to the deep part of the skin is small.
[0031]
[Embodiment of the Invention] Although an example is hung up over below and this invention is explained to it in more detail, this invention is not limited only to these examples.
[0032] [Preparation of an acrylic copolymer (A)] Dodecyl methacrylate 2286g, 2-ethylhexyl methacrylate 14256g, 2-ethylhexyl acrylate 1656g, hexanedioldimethacrylate 2.3g, and 8500g of ethyl acetate were put into 40l. curing units, and it heated at 80 degrees C. Subsequently, the acrylic copolymer (A) solution of weight average molecular weight 1.05x106 and 58 % of the weight of solid content was obtained by adding into this mixed liquor, dividing the solution which dissolved lauroyl peroxide 16g in cyclohexane 1500g, and performing a polymerization reaction into it over 6 hours.
[0033] [Preparation of an acrylic copolymer (B)] Butyl acrylate 70g, 2-ethylhexyl acrylate 130g, hexanedioldimethacrylate 0.025g, and 136g of ethyl acetate were put into curing units, and it heated at 60 degrees C. Subsequently, the acrylic copolymer (B) solution of the viscosity of 350,000cps and 59 % of the weight of solid content was obtained by adding into this mixed liquor, dividing the solution which dissolved lauroyl peroxide 0.6g in cyclohexane 10g, and performing a polymerization reaction into it over 10 hours.
[0034] [Preparation of a rubber system binder (C) solution] Styrene-isoprene-styrene / block-copolymer (SIS) [16 "caliph REXX TR1107" by shell chemistry company] weight section, The polybutene (Nippon Oil Co., Ltd. make, average molecular weight 1350) 5 weight section, the alicycle group saturated hydrocarbon resin ("Al Cong P90" by Arakawa chemistry company) 36.5 weight section, The liquid paraffin 42.5 weight section and the butylhydroxytoluene 0.6 weight section were put in in the mixing chamber, under the nitrogen-purge ambient atmosphere, it heated at 150 degrees C, dissolution mixing was carried out, and the rubber system binder (C) was prepared.
[0035] The acrylic copolymer of the loadings shown in Table 1 (A), (Examples 1-5, examples 1-9 of a comparison) (B) As a rubber system binder (C) and a drug, or indomethacin, nitroglycerin, or estradiol, As fatty alcohol, it put into the silicic anhydride as myristic-acid isopropyl and a bulking agent, ethyl acetate was put into the mixing chamber as a diluent as cetyl alcohol (method article of an office), and a plasticization agent, it mixed to homogeneity with the dissolver, and the medical-application adhesiveness constituent of 30 % of the weight of nonvolatile matters was obtained. By the knife coating machine, this binder layer was obtained on the polyethylene terephthalate film (base material) with a thickness of 38 micrometers, and coating and after drying and forming a binder layer, lamination and patches were obtained for this adhesive constituent to the with a thickness of 31 micrometers ethylene-vinylacetate copolymer side of polyester / ethylene-vinylacetate copolymer laminated film.
[0036] About the patches obtained in the above-mentioned example and the example of a comparison, the following performance evaluation was performed and the result was shown in Tables 2 and 3.
(1) The skin translucency test of a drug release sex-test hair loess mouse (a male, 7 weeks old) performed. The regions-of-back extraction skin of a hair loess mouse was fixed to Francis's diffusion cel, and the patches pierced 3.14cm to the skin up side 2 (round shape with a diameter of 2cm) were stuck as a test piece. The receptor liquid prepared in the skin bottom till after [pasting] 24 hours was sampled with time, and the amount of drugs in liquid was measured by high-speed liquid chromatography. The diffusion cel was set as the constant temperature of 37 degrees C, and the physiological saline adjusted to pH7.2 was used for receptor liquid. in addition, drug release nature

boiled and showed the amount of drug transparency (indomethacin = 26.2microg/cm2, nitroglycerin =1305microg/cm2) 24 hours after being measured by the patches of the examples 4 and 6 of a comparison by the relative value set to 100. Moreover, after [2, 6, and 20] pasting and the amount of drug transparency in 24 hours (mug/cm2) were shown in Table 3 about examples 2 and 3 and the examples 4-7 of a comparison.

[0037] (2) Stimulus sex-test patches were cut in the magnitude of 2 (round shape with a diameter of 2cm) 3.14cm, and it considered as the test piece. this test piece -- the abdomen of a guinea pig (a male, 5 weeks old) -- 24 hours -- sticking -- the erythema generation condition of the pasting section skin 30 minutes after exfoliation -- viewing -- observing -- the generation condition of erythema -- Draiz -- law (1959FDA, 1973Federal Register) estimated. The trial was performed by n= 6 (1 per one test piece) sample, the score was given in accordance with the following criterion, and the average of a score was made into the skin stimulation index.

With no erythema all ** .... Erythema very slight zero point .... One point (erythema of extent accepted at last)

Clear erythema .... Whenever [middle / of two point], thru/or strong erythema .... Incrustation light to the strong erythema of three-point deep red .. Four points [0038] (3) It exfoliated, after sticking the same test piece as a sticky trial (2) on the abdomen of a guinea pig (a male, 5 weeks old) for 24 hours, and visual observation of the existence of the paste remainder was carried out. The number (molecule) which had the paste remainder among n= 6 samples (denominator) was shown in front Naka. In addition, formation of an edema or scab did not have ****** at this trial.

[0039]

[Table 1]

		粘着剤組成物 (重量%)			
		共重合体又は粘着剤 (種類)	セチルアルコール	薬物 (種類)	添加物 (種類)
実施例	1	95 (A)	5	-	-
	2	92 (A)	5	3 (IMT)	-
	3	80 (A)	2	18 (GTN)	-
	4	83 (A)	2	5 (E2)	10 (IPM)
	5	90 (A)	1	-	9 (珪酸)
比較例	1	100 (A)	-	-	-
	2	90 (A)	-	-	10 (IPM)
	3	95 (B)	5	-	-
	4	97 (A)	-	3 (IMT)	-
	5	91.9 (C)	5	3 (IMT)	0.1 (BHT)
	6	82 (A)	-	18 (GTN)	-
	7	80 (B)	2	18 (GTN)	-
	8	85 (A)	-	5 (E2)	10 (IPM)
	9	83 (B)	2	5 (E2)	10 (IPM)

IMT:インドメタシン、GTN:ニトログリセリン
E2 :エストラジオール、IPM:ミリスチン酸イソプロピル
BHT:ブリルヒドロキシトルエン

[0040]

[Table 2]

		薬物放出性	貼付性試験（糊残り数）	皮膚刺激指数（点）
実施例	1	－	0／6	1.17
	2	137	0／6	1.33
	3	128	0／6	1.17
	4	141	1／6	1.33
	5	－	0／6	1.00
比較例	1	－	0／6	2.33
	2	－	0／6	2.67
	3	－	0／6	2.00
	4	100	0／6	2.17
	5	118	0／6	2.33
	6	100	0／6	2.33
	7	72	3／6	2.00
	8	100	1／6	2.50
	9	93	4／6	2.17

[0041]
[Table 3]

		薬物放出性の経時変化（μg／cm²）			
		2時間後	6時間後	20時間後	24時間後
IMT	実施例2	2.9	8.8	29.4	34.8
	比較例4	2.1	6.5	21.9	26.2
	比較例5	2.9	8.9	29.6	35.3
GTN	実施例3	125	424	1387	1670
	比較例6	104	319	1075	1305
	比較例7	76	233	776	940

ＩＭＴ：インドメタシン、ＧＴＮ：ニトログリセリン

[0042]
[Effect of the Invention] The adhesive constituent of this invention is as above-mentioned, and discovers adhesiveness sufficient during pasting, there are few skin stimuli, and since drug release nature is excellent, it is suitably used as a binder of patches.

[Translation done.]